REMARKS

Claims 1, 4-34, 36, 45, 46, 86-90, 157-181, 183, 212, 213, 263-267 and 280-296 are pending in the application. In the Office Action mailed May 16, 2006, claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265 and 280-296 are rejected (claims 46, 88, 212-213 and 266-267 having been withdrawn from consideration as drawn to non-elected species).

Consideration of the following remarks is respectfully requested.

APPLICANTS' INTERVIEW SUMMARY

Applicants thank Primary Examiner Frank Lu for the courtesies extended during the telephone interview on August 18, 2006 (hereinafter "the Interview") with Applicants' representatives Adriane M. Antler and Weining Wang. During the interview, the Office Action mailed May 16, 2006 was discussed. In response to Ms. Antler's inquiry regarding the bases for the rejection under 35 U.S.C. § 112, second paragraph, the Examiner indicated that he was not certain whether measurements of exons/multiexons and exon variants could be carried out in a solution. Ms. Antler proposed to describe in the response different methods known in the art that can be used to carry out the measurements including in a solution. The Examiner indicated that he would consider the response.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-293 and 293-296 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claim 1 is rejected as being incomplete for omitting essential steps. The Examiner contends that the omitted steps are how to measure the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes and how to measure the expression level of each of a plurality of different variants of said exon in one gene "because both above measurements cannot be finished in a solution" (Office Action, page 3).

Applicants respectfully point out that claim 1 is directed to a method for analyzing exon expression in a cell sample. The method comprises measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a

plurality of different genes in the genome of an organism from which said cell sample is derived. Among the plurality of different genes, at least one gene has an exon having a plurality of different variants. The claimed method further comprises measuring the expression levels of different variants of this exon. Thus, the claimed invention is a method for analyzing exon expression in a sample by not only measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes but also measuring the expression levels of different variants of an exon of at least one of the genes. Such a method allows determination of not only expression of individual exons and individual multiexons but also expression of exon variants in a cell sample. Therefore, the basic steps of the method are (a) measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes, and (b) for an exon (of at least one of the different genes) having a plurality of different variants, measuring the expression levels of different variants of this exon. A person skilled in the art would understand that the claim clearly defines the metes and bounds of the invention.

Applicants respectfully point out that there are many methods known in the art that can be used for measurements of the expression levels of gene sequences, e.g., exons, multiexons, and exon variants. For example, expression levels of sequences in a transcript can be measured using DNA microarrays. The specification provides a detailed description of how to perform such measurements using polynucleotide probe arrays (see, Section 5.4 of the specification at page 35, line 16 through page 51, line 15). Other methods that are commonly known in the art and that can be used to measure the expression levels of gene sequences include, but not limited to, real-time reverse transcription PCR (real-time RT-PCR), an RNase protection assay, and Northern blotting. One skilled in the art, in view of the teachings of the specification, would be able to employ these methods in a straightforward manner to carry out the claimed invention.

For example, in a real-time RT-PCR assay, primers specific for the sequence fragments of interest (which in this instance would be, for example, exon sequences) are used to amplify the sequence fragments. The amplified sequence fragments are then detected, e.g., by using probes that are complementary and hybridizable to sequences in the amplified sequence fragments (in this instance, e.g., exon specific and/or junction specific probes). Detection of amplification products allows determination of the levels of sequence fragments.

See, e.g., the following prior art references which teach real-time RT-PCR: Bustin, 2000, J. Mol. Endocrinology 25:169-193, published in the October 2000 issue, hereinafter "Bustin", e.g., first paragraph, left column on page 186, and FIG. 8, right column on page 186 (submitted as reference C01 in the Supplemental Information Disclosure Statement submitted concurrently with this response); Martell et al., 1999, J. Clin. Micro. 37:327-332 (submitted as reference C02 in the Supplemental Information Disclosure Statement submitted concurrently with this response); Kafert et al., 1999, Anal. Biochem. 269:210-213 (submitted as reference C03 in the Supplemental Information Disclosure Statement submitted concurrently with this response); Robinson et al., 1997, Gene 198:1-4 (submitted as reference C04 in the Supplemental Information Disclosure Statement submitted concurrently with this response). Moreover, real-time RT-PCR can be carried out in a solution, e.g., by using probes labeled with fluorescence labels that fluoresce only upon hybridization or using fluorescence dyes that fluoresce only upon binding to double stranded amplification products, and detecting the labeled probes or fluorescence dyes directly in the solution containing the amplification products using a spectrometer (see, e.g., Bustin, the section entitled "Instrumentation" beginning on page 173, bottom of the left column; Martell et al., 1999, J. Clinical Microbiology 37:327-332). Real-time RT-PCR can also be carried out by methods in which the amplified sequence fragments are detected using electrophoresis (see, e.g., Kafert et al., 1999, Anal. Biochem. 269:210-213; Robinson et al., 1997, Gene 198:1-4).

One skilled in the art could also use an RNase protection assay, in which one or more probes that are complementary and hybridizable to different sequence fragments in an mRNA, e.g., fragments containing different exons, are hybridized to the mRNA. Hybridization of the probes to the mRNA protects the mRNA fragments from subsequent RNase digestion. After RNase digestion, the protected fragments can be detected to determine the levels of the expressed exons in the mRNA. See, e.g., Lollmann et al., 1997, Biochem. Biophys. Res. Comm. 238:648-652, first paragraph, left column, page 649 (submitted as reference C05 in the Supplemental Information Disclosure Statement submitted concurrently with this response); and Fei et al., 1997, Proc. Natl. Acad. Sci. USA 94:7001-7005, third paragraph, left column, page 7002 (submitted as reference C06 in the Supplemental Information Disclosure Statement submitted concurrently with this response, hereinafter "Fei"), which teach RNase protection assays.

One skilled in the art could also use a Northern blot assay, in which cDNA probes, which could be, e.g., exon specific and/or junction specific cDNA probes, are hybridized to a Northern blot. Detection of the probes allows determination of the levels of expression (see, e.g., Fei, second paragraph, right column, page 7001).

A person skilled in the art would understand that the above-described methods as exemplified in the prior art references are generally applicable for determination of sequences in a transcript, including exons and exon variants, e.g., by designing appropriate primers and/or probes. A person skilled in the art would also understand that none of such specific methods for measuring the expression levels of sequences in a transcript are essential steps of the claimed method because the claimed method is not limited to any such specific methods. The meaning of the steps presently recited in the claims would also be clear to the skilled person, since he/she would understand that any of the methods known in the art could be used to carry out the steps.

With respect to carrying out the measurements in a solution, Applicants respectfully point out that the measurement steps, i.e., the measurement of the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes and the measurement of the expression levels of different variants of this exon, can be carried out in a solution. For example, as discussed above, in real-time RT-PCR, not only the amplification occurs in a solution, but the detection of amplicon levels can also be achieved in the same solution by using probes labeled with fluorescence labels and detecting the labeled probes directly in the solution containing the amplification products using a spectrometer (see, e.g., Bustin, the section entitled "Instrumentation" beginning at the bottom of the left column on page 173).

Applicants also respectfully point out that the claimed method is not limited to performing measurements in a solution. As discussed above, although real-time RT-PCR can be carried out in a solution, it can also be carried out by methods in which the amplified sequence fragments are detected using electrophoresis. In a DNA microarray assay, hybridization reactions occur on a substrate contacted with a hybridization solution, and determination of hybridization levels is achieved by detecting the probes on the substrate. In both an RNase protection assay and Northern blotting, electrophoresis may be employed to detect the probes. Thus, the measurements can be carried out in a variety of different manners.

Because the claimed methods are not limited to performing the measurements using a specific method, Section 112, second paragraph, does not require that the claims recite any such specific method as an essential step. It has long been established that a method claim may be patentable irrespective of the particular form of the instrumentalities used. For example, in *Cochrane v. Deena* the Supreme Court has held

> [t]hat a process may be patentable, irrespective of the particular form of the instrumentalities used, cannot be disputed. If one of the steps of a process be that a certain substance is to be reduced to a powder, it may not be at all material what instrument or machinery is used to effect that object, whether a hammer, a pestle and mortar, or a mill. Either may be pointed out; but if the patent is not confined to that particular tool or machine, the use of the others would be an infringement, the general process being the same. A process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing. .... The process requires that certain things should be done with certain substances, and in a certain order; but the tools to be used in doing this may be of secondary consequence.

Cochrane v. Deena, 94 U.S. 780, 787-788 (1876). In the present case, the claimed method is a method for analyzing exon expression in a sample by not only measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes but also measuring the expression levels of different variants of an exon of at least one of the genes. A person skilled in the art would understand that, for such a method, all that matters is to make the two measurements so that expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes and the expression levels of different variants of an exon of at least one of the genes are obtained, and that whether the measurements are carried out in a solution and/or what instrumentalities are used is of no significance.

Thus, Applicants respectfully submit that the claims do not contain gaps, and that the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

CLAIMS WITHDRAWN FROM CONSIDERATION AS BELONGING TO NON-ELECTED SPECIES SHOULD BE CONSIDERED

Claims 46, 88, 212, 213, 266 and 267 are withdrawn from consideration by the Examiner as belonging to non-elected species. Since Applicants believe that the generic claims are allowable, claims 46, 88, 212, 213, 266 and 267 should be considered by the Examiner. Applicants respectfully request that these claims be considered by the Examiner.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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